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<p>(54) Title: CHEWABLE SOFT CAPSULE</p> <p>(57) Abstract</p> <p>The present invention comprises chewable, soft gelatin capsules having a sheath formed of a mixture of a low bloom and a medium bloom gelatins, a plasticizer, water, and preferably a moisture retention agent to enhance the machinability and integrity of the sheath composition; and a fill of an active material in a carrier liquid.</p>		

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## CHEWABLE SOFT CAPSULE

Background of the Invention5    (1) Field of the Invention

The present invention relates generally to soft gelatin capsules and to a process for their preparation, and in particular to soft gelatin capsules having a chewable consistency.

(2) Description of the Prior Art

10       Soft gelatin capsules are comprised of a gelatin sheath encapsulating a fill of a medicament, vitamin, or other material to be consumed by the user. The one-piece gelatin sheath or shell includes a plasticizer, normally glycerin or sorbitol, to control the softness and flexibility of the sheath. The sheath also includes water, and optionally, other additives, such as flavorants. The fill is normally comprised of a carrier in which the active material is dissolved or suspended.

15       Chewable soft gelatin capsules, or chewable softgels, are designed so that the user chews upon the capsule to release the fill into the mouth instead of swallowing the capsule with the fill still encapsulated within the sheath. Chewable capsules are particularly suitable for administering analgesics, vitamins, minerals and cold remedies. After the fill has been released, the user chews the fractured sheath until it is partially or completely dispersed. In an alternative  
20       embodiment described in U.S. Patent No. 4,428,927, a chewing gum base material is incorporated into the sheath and the sheath is not made for swallowing.

          Therefore, acceptable sheath formulations must not only have sufficient integrity to encapsulate the fill without leakage prior to consumption, they must also be readily soluble or dispersible when chewed. In addition, the formulations must not be of a sticky or tacky nature  
25       during processing, interfering with the conversion of the gelatin mass into sheaths in conventional encapsulation equipment.

While an effective delivery system, the acceptance of chewable softgels has been limited by the mouth-feel or texture of the sheath, which is commonly perceived to be leathery or rubbery, and the difficulty in consuming the fractured sheaths after the fill has been released. The use of chewable softgels could be significantly expanded if this problem could be overcome.

5

### Summary of the Invention

The present invention is directed to chewable soft gelatin capsules, or chewable softgels comprised of a chewable gelatin sheath encapsulating a liquid fill. The sheath composition is specifically characterized by flexibility and a non-sticky consistency so that it can be formed into capsules using conventional encapsulation machinery, and the integrity to enclose a fill for an extended period of time, e.g., up to about two years, without dissolution or leakage, while still being readily soluble upon consumption.

Most conventional softgel capsules are produced by a rotary die process in which a molten mass of a gelatin sheath formulation is fed from a reservoir onto drums to form two spaced sheets or ribbons of gelatin in a semi-molten state. These ribbons are fed around rollers and brought together at a convergent angle into the nip of a pair of roller dies that include opposed die cavities. A liquid or paste medicament or other material to be encapsulated is fed into the wedge-shaped joinder of the ribbons.

The gelatin ribbons are continuously conveyed between the dies, with portions of the medicament being trapped between the sheets inside the die cavities. The sheets are then pressed together, and severed around each die so that opposed edges of the sheets flow together to form a continuous gelatin sheath around the entrapped medicament. The part of the gelatin sheet that is severed from the segments forming the capsules is then collected for recycling. The very soft

capsules are then dried to increase the integrity of the sheath, and packaged for later distribution and consumption.

Manufacture of uniform soft gelatin capsules by this or similar processes requires a sheath material that has good "machineability," i.e., it is of critical importance that the sheath material be of a non-tacky or non-sticky nature, so that the sheath material can be brought into  
5 contact with the rollers without sticking. At the same time, the sheath composition must not degrade or dissolve during storage prior to consumption, allowing the fill material to leak from the capsule.

The properties of the sheath material is determined in significant part by the cohesive  
10 strength of the constituent gelatin, expressed as "bloom." Conventional soft gelatin capsules normally have a bloom in the range of from about 150 to about 275. This bloom value is determined by measuring the weight in grams required to move a plunger 0.5 inch in diameter, 4 mm into a 6.67% gelatin gel that has been held for 17 hours at 10°C.

Chewable softgel capsule sheaths are designed to at least partially disperse or dissolve in  
15 the user's mouth within a brief period of time after the fill contents have been released, e.g., within about 60 seconds, so that it can be swallowed. Therefore, in addition to the above properties, the sheath of these products must also be soluble after the fill contents are released. The sheath should also have a good "mouth feel." As used herein, "mouth feel" describes chewability. Chewing the sheath should be a pleasant, or at least not an unpleasant sensation that  
20 results in a swallowable composition.

Surprisingly, it has been found that a chewable softgel sheath having all of these desired characteristics can be produced from a specific mixture of defined gelatins in combination with defined percentages of a plasticizer and preferably a moisture retaining agent. This combination

of ingredients, to be described herein in detail, has been found to produce capsule sheaths that have the necessary low stickiness for machineability, and sufficient integrity for stable fill encapsulation, while having a desirable mouth-feel and solubility.

More specifically, the present capsule sheaths are formed of a mixture of a first gelatin  
5 having a bloom substantially lower than the bloom of gelatins conventionally used to form capsule sheaths, in combination with a minor percentage of a second gelatin having a bloom within the range of conventional sheath-forming gelatin blooms. The first gelatin has insufficient integrity for use alone in sheath formation.

Plasticizers are essential in sheath formulations in order to impart the necessary softness  
10 and flexibility to the sheath material, so it can be formed into capsules. The presence of a significant percentage of plasticizer, however, may result in a sheath that is difficult to process because the sheath will stick to the rollers during machining, as described herein above. Also, the plasticizers tend to dry out the sheath over any extended shelf-life of the finished product capsule, resulting in a capsule with a "leathery" mouth feel.

15 In accordance with an additional embodiment of the present invention, the tackiness or stickiness of the sheath can be maintained at a desired machinable level, even in the presence of high percentages of plasticizers, by adding a small percentage of a moisture retention agent, as hereafter defined, to the sheath composition. The moisture retention agent also maintains the desired mouth feel over an extended shelf-life.

20 While the function of the moisture retention agent is not entirely clear, it appears that the additive disrupts the gelatin structure to reduce the gelatin strength and immobilizes or retains water.

More specifically, the present sheath composition is comprised of a first gelatin, hereinafter referred to as "low bloom" gelatin, having a bloom of up to about 100, and preferably from about 80 to about 100. The low bloom gelatin is combined with a second gelatin, hereinafter referred to as "medium bloom" gelatin, having a bloom in the range of from about 150 to about 275, and preferably from about 150 to about 175. The first and second gelatins preferably are present in a ratio of from about 1:1 to about 10:1, and even more preferably a ratio of from about 3:1 to about 5:1. Type A or B gelatins or a mixture thereof, may be used for the first and/or the second gelatin. Limed bone, acid bone, fish and/or pig skin gelatins may be used in the present invention.

10 The sheath plasticizer preferably is glycerin, sorbitol, maltitol, or a mixture thereof. Other plasticizing agents known in the art to improve softness and flexibility are also within the scope of the present invention. The sheath will normally include at least about 10 percent by weight plasticizer in order to impart the desired softness and flexibility. Preferably, from about 20 to about 30 percent by weight of plasticizer will be employed.

15 As noted earlier, when the required percentages of plasticizer are combined with the above-described gelatin mixture, the capsule may not have desired machinability or extended chewability characteristics. However, it has been found these characteristics are improved by adding at least about 0.5 % by weight, and preferably from about 1 to about 5 % by weight of a moisture retention agent to the composition.

20 Materials used in the present invention as moisture retention agents have been previously added to sheaths used to encapsulate water miscible, volatile fills, see, e.g., United States Patent No. 4,804,542. In these prior art compositions, the materials are used to prevent dissolution of the sheath by the particular fills used. In the present invention, however, the moisture retention

agent serves a different purpose, namely, to improve machinability and prevent the sheath of the finished capsule from drying out. In addition, the moisture retention material finds use in both water miscible, volatile fills, and with carriers of the type described below, where such materials have not previously been used or required.

- 5           Although not meant to limit the scope of the present invention, examples of moisture retaining agents include celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide. Specific stabilizers are: starches such as LO-TEMP®, SOFT-SET®, OR MIRA-GEL® manufactured by A.E. Staley Manufacturing Company of Decatur, IL.; microcrystalline cellulose such as
- 10    AVICEL® manufactured by FMC corporation of Philadelphia, PA.; silicon dioxide such as AEROSIL® manufactured by Degussa Aktiengesellschaft of Frankfurt, Germany; and cellulose such as SOLKA FLOC® manufactured by Fiber Sales & Development Corporation of Urbana, OH.

- Other sheath ingredients may include taste modifiers. For example, non-reducing sugars,
- 15    such as xylitol, maltitol, or LYCASIN® manufactured by Roquette America, Inc. of Keokuk, IA, are commonly added to the composition. These non-reducing sugars are usually added in amounts up to about 10% of the sheath composition.

Thus, the preferred sheath compositions of the present invention are comprised of the following ingredients in the specified percentages:

INGREDIENT	% BY WEIGHT
Low Bloom Gelatin	15-30
Medium Bloom Gelatin	5-15
Plasticizer	20-40
Water	10-30
Moisture Retaining Agent	0.5-5
Other Ingredients	0-10

20



It will be understood that different percentages may be selected within the above ranges so that the sum of the percentages of the sheath ingredients is equal to 100%. If additional ingredients are used, the percentages will be adjusted within the ranges listed to accommodate  
5 the additional ingredients.

Based upon the preferred composition described immediately hereinabove, upon casting the sheath into gelatin capsules it is known in the art that the drying process will reduce the water content of the sheath to less than about 10%, with a preferred industry standard of about 6% to about 8%. Accordingly, the capsule sheath formed from the above mixture, after being dried for  
10 storage and subsequent use, preferably is comprised of the following ingredients in the specified parts by weight:

INGREDIENT	PARTS BY WEIGHT
Low Bloom Gelatin	20-38
Medium Bloom Gelatin	6-20
Plasticizer	26-52
Water	6-8
Moisture Retaining Agent	0.60-6.50
Other Ingredients	0-13

The capsule fill is generally comprised of a liquid carrier, and an active ingredient dissolved or suspended therein. The liquid carrier preferably is a water-immiscible liquid such  
15 as a vegetable and aromatic oils, aromatic and aliphatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, high molecular weight organic acids and alcohols, or lower molecular weight polyalkylene glycols, such as polyalkylene glycol 600. Other embodiments may contain water-miscible liquid carriers as well.

As used in the present description, the term "active ingredient" is intended to include  
20 medicaments, vitamins, minerals, fruits, herbals and other encapsulatable materials or

combinations thereof understood by those skilled in the art to support the desired effect. For example, if the effect desired is mineral supplementation, exemplary active ingredients may be calcium, magnesium and Vitamin D. Additionally, if the desired effect is targeted toward urinary tract health, an exemplary active ingredient of cranberry is included.

5           The fill may also include other ingredients, such as sweeteners and other flavorants, or flavor modifiers. Suitable flavor modifiers include any natural or artificial flavor or a combination thereof. Also, as is known in the industry, WONF (with other natural flavors) flavorants may be included.

          Generally, the active ingredient will be present in an amount of from up to about 50% by weight, with variations allowed for the variable fill employed. Mixtures of active ingredients  
10           may also be incorporated into the fill.

#### EXAMPLES

          The following examples describe the manufacture and testing of various sheath formulations for acceptable chewability, and for low tack or stickiness. Chewability is a  
15           subjective test in which chewability is evaluated by considering such factors as the mouth feel of the capsule, and the ease of dissolution or dispersion in the mouth and the ease of swallowing the fractured sheath.

          The tendency of the sheath to stick to rollers is estimated with the use of a texture analyzer in which the force (g) required to remove the gelatin sheath from a simulated casting  
20           machine is measured. As a base line requirement for the preferred embodiment of the present invention, a value of 35 g or less was established based upon testing conventional gelatin sheath compositions. The preferred texture is variable depending upon the specific manufacturing process employed. As discussed above, most softgels are manufactured through a rotary die

process, however, the present invention should not be limited thereto. Other appropriate manufacturing processes are also within the scope of this invention.

As will be seen from the Examples, the chewability and machineability of a given sheath formulation is dependent upon the combination of gelatins used, the amount of plasticizer, and  
5 the presence and amount of a moisture retention agent. The optimum percentages of each ingredient will depend upon the overall formulation contents, and the identity of the individual ingredients. However, evaluation and selection of the most desirable formulation will be well within the skill of practitioners in this area, once they are familiar with the present disclosure.

For Tables 1 and 2, the following abbreviations are used: S-S for SOFT-SET®; L-T for  
10 LO-TEMP®; Sorb for Sorbitol; Aero for AEROSIL®; Avi for AVICEL®; and S-F for SOLKA FLOC®, each component being described more fully above.

**TABLE 1 Experiments 1-10**

COMPONENT	1	2	3	4	5	6	7	8	9	10
100 Bloom	31.7	30.6	23.1	23.1	23.13	23.54	23.54	24.13	23.54	26.54
150 Bloom		5.1	12.5	12.5	12.54	10	6	6	10	6
275 Bloom										
Glycerin	24	24	29.9	29.9	29.9	29.9	29.9	29.9	26.9	26.9
Water	15.1	18.7	25.7	25.7	25.7	25.4	29.9	25.77	25.77	25.77
Lycasin® - 75% Solids		20.7	6.5	6.5	3.28	3.28	3.28	6.28	3.28	5.83
Xylitol						4.83	3.28	5.28	3.28	3.28
Crystallized Fructose		2.9			3.28					
Starch			2 S-S	2 L-T		3 L-T	3 L-T	2 L-T	3 L-T	3 L-T
Cellulose										
Other					2 Pectin		5.54 Sorb	0.55 Aero	4.13 Sorb	4.13 Sorb
Texture Analyzer (g)	1050	800	28.5	25.5	19.7	19	20	21	23.5	15.1

TABLE 1a	COMMENTS
Exp. 1	Very tacky and sticky
Exp. 2	Very tacky and sticky
Exp. 3	Added additional water; Performance OK
Exp. 4	Texture and chewability acceptable
Exp. 5	Too much self tack
Exp. 6	Excellent texture and chewability characteristics
Exp. 7	Chewability was great, but very self-tacky
Exp. 8	Gel was acceptable
Exp. 9	Performance was good, but tough with time
Exp. 10	Excellent gel texture and chewability

TABLE 2 Experiments 11-20

COMPONENT	11	12	13	14	15	16	17	18	19	20
100 Bloom	23.13	23.12	26.54	24	24	23	23	23	25	25
150 Bloom	12	12	6	6	12	12	8	6		
275 Bloom									5	5
Glycerin	26	26	26.9	27	26	26	26	26	30	28.5
Water	25.77	25.77	25.77	26	25.77	26	29	30	30	30
Lycasin® - 75% Solids	7.27	3.28	5.28	7.3	7	7	7	7	4	4
Xylitol	3.38	3.28	3.28	6.3	3	5	5	5	4	4
Crystallized Fructose										
Starch	2 L-T	2 L-T	3 L-T	2 L-T	2 L-T					
Cellulose						1 S-F	2 Avi	3 Avi	2 S-F	3.5 Avi
Other	.544 Aero	3.98 Sorb	4.13 Sorb	1 Sorb	2.26 Aero					
Texture Analyzer (g)	19	18	14.9	15	13	38	15	11	19	25

Table 2a	COMMENTS
Exp. 11	Gel was very tough initially
Exp. 12	Acceptable performance
Exp. 13	Excellent chewability, self-tack may be a problem
Exp. 14	Acceptable performance
Exp. 15	Acceptable performance
Exp. 16	Too sticky
Exp. 17	Excellent texture analyzer and chewability characteristics
Exp. 18	Excellent texture analyzer and chewability characteristics
Exp. 19	Excellent texture analyzer and chewability characteristics
Exp. 20	Acceptable texture and chewability characteristics

Certain modifications and improvements will occur to those skilled in the art upon a reading of the foregoing description. It should be understood that all such modifications and improvements have been deleted herein for the sake of conciseness and readability but are properly within the scope of the following claims.

What is claimed is:

1. A gelatin capsule sheath suitable for enclosing a fill comprised of:
  - a) a first gelatin having a bloom strength of up to about 100;
  - b) a second gelatin having a bloom strength of at least about 150; and
  - 5 c) a plasticizer in an amount sufficient to render said sheath flexible.
2. The sheath of claim 1, further including a moisture retention agent in an amount sufficient to provide sheath integrity.
- 10 3. The sheath of claim 1, wherein said first and second gelatins are present in a ratio of from about 1:1 to about 10:1.
4. The sheath of claim 1, wherein said first gelatin is present in an amount for from about 20 to about 38 % by weight of said sheath.
- 15 5. The sheath of claim 1, wherein said second gelatin is present in an amount for from about 6 to about 20% by weight of said sheath.
6. The sheath of claim 1, wherein said plasticizer is present in an amount of up to 52% by
- 20 weight of said sheath.
7. The sheath of claim 1, wherein said plasticizer is selected from the group consisting of glycerin, sorbitol, maltitol and mixtures thereof.

8. The sheath of claim 2, wherein said moisture retention agent is present in an amount of from about 0.6 to about 6.5% by weight of said sheath.
9. The sheath of claim 2, wherein said moisture retention agent is selected from the group  
5 consisting of celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide.
10. The sheath of claim 1, including up to about 10% by weight water.
- 10 11. A chewable, gelatin capsule with a continuous soft sheath encapsulating a fill, said sheath being comprised of:
- a) a first gelatin having a bloom strength of up to about 100;
  - b) a second gelatin having a bloom strength of at least about 150;
  - c) a plasticizer in an amount sufficient to render said sheath flexible; and
  - 15 d) a moisture retention agent in an amount sufficient to provide sheath integrity.
12. The capsule of claim 11, wherein said fill includes a carrier selected from the group consisting of vegetable and aromatic oils, aromatic and aliphatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, high molecular weight organic acids and alcohols, or  
20 lower molecular weight polyalkylene glycols.
13. The capsule of claim 11, wherein said fill includes an active ingredient.



14. The capsule of claim 13, wherein said active ingredient is selected from the group consisting of medicaments, vitamins, minerals, fruits and herbals.
15. The sheath of claim 11, wherein said first and second gelatins are present in a ratio of  
5 from about 1:1 to about 10:1.
16. The sheath of claim 11, wherein said first gelatin is present in an amount for from about  
20 to about 38 parts by weight of said sheath.
- 10 17. The sheath of claim 11, wherein said second gelatin is present in an amount for from  
about 6 to about 20 parts by weight of said sheath.
18. The sheath of claim 11, wherein said plasticizer is present in an amount of up to 52 parts  
by weight of said sheath.
- 15 19. The sheath of claim 11, wherein said plasticizer is selected from the group consisting of  
glycerin, sorbitol, maltitol, and mixtures thereof.
20. The sheath of claim 11, wherein said moisture retention agent is present in an amount of  
20 from about 0.60 to about 6.50 parts by weight of said sheath.

21. The sheath of claim 11, wherein said moisture retention agent is selected from the group consisting of celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide.
- 5 22. The sheath of claim 11, including from about 6 to about 8 parts by weight water.
23. A gelatin capsule sheath comprised of:
- a) from about 20 to about 38 % by weight of a first gelatin having a bloom of from about 80 to about 100;
  - 10 b) from about 6 to about 20 % by weight of a second gelatin having a bloom of from about 150 to about 275;
  - c) up to about 10% water;
  - c) a plasticizer in an amount sufficient to render said sheath flexible; and
  - d) a moisture retention agent in an amount sufficient to provide sheath integrity.
- 15
24. The sheath of claim 23, wherein said plasticizer is selected from the group consisting of glycerin, sorbitol, maltitol, and mixtures thereof.
25. The sheath of claim 23, wherein said plasticizer is present in an amount of from about 26
- 20 to about 52 % by weight of said sheath.

26. The sheath of claim 23, wherein said moisture retention agent is selected from the group consisting of celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide.

5 27. The sheath of claim 23, wherein said moisture retention agent is present in an amount of from about 0.6 to about 6.5 % by weight of said sheath.

28. A chewable, gelatin capsule with a continuous soft sheath encapsulating a fill, said sheath including

- 10 a) from about 20 to about 38 parts by weight of a first gelatin having a bloom of from about 80 to about 100;
- b) from about 6 to about 20 parts by weight of a second gelatin having a bloom of from about 150 to about 275;
- c) from about 6 to about 8 parts by weight of water;
- 15 c) a plasticizer in an amount sufficient to render said sheath flexible; and
- d) a moisture retention agent in an amount sufficient to provide sheath integrity.

29. The capsule of claim 28, wherein said fill is comprised of a carrier liquid and an active material.

20

30. The capsule of claim 29, wherein said carrier liquid is a water-immiscible liquid selected from the group consisting of vegetable and aromatic oils, aromatic and aliphatic and aliphatic

hydrocarbons, chlorinated hydrocarbons, ethers, esters, high molecular weight organic acids and alcohols, and lower molecular weight polyalkylene glycols.

31. The capsule of claim 29, wherein said moisture retention agent is selected from the group  
5 consisting of celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide.

32. The capsule of claim 29, wherein said active material is selected from the group consisting of medicaments, vitamins, minerals, fruits, and herbals.

10

33. A method for forming a chewable gelatin sheath comprising:

- a) providing a mixture of about 15 to about 30 % by weight of a first gelatin having a bloom of from about 80 to about 100, from about 5 to about 15 % by weight of a second gelatin having a bloom of from about 150 to about 275, from about 10 to about 30 water, and an amount  
15 of a plasticizer sufficient to render said sheath flexible; and  
b) forming a film from said mixture.

34. The method of claim 33, wherein said mixture further includes a moisture retention agent in an amount sufficient to provide sheath integrity.

20

35. The method of claim 33, wherein said plasticizer is selected from the group consisting of glycerin, sorbitol, maltitol, and mixtures thereof.

36. The method of claim 33, wherein said plasticizer is present in an amount of from about 20 to about 40 % by weight of said mixture.

37. The method of claim 33, wherein said moisture retention agent is selected from the group consisting of celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide.

38. The method of claim 34, wherein said moisture retention agent is present in an amount of from about 0.5 to about 5 % by weight of said sheath.

10

39. A method for manufacturing chewable soft gelatin capsules comprising:

- a) providing a mixture of about 15 to about 30 % by weight of a first gelatin having a bloom of from about 80 to about 100, from about 5 to about 15 % by weight of a second gelatin having a bloom of from about 150 to about 275, from about 10 to about 30 water, and an amount of a plasticizer sufficient to render said sheath flexible; and
- b) encapsulating a fill with said mixture.

15

40. The method of claim 39, wherein said mixture further includes a moisture retention agent in an amount sufficient to provide sheath integrity.

20

41. The method of claim 39, wherein said fill includes a carrier liquid selected from the group consisting of vegetable and aromatic oils, aromatic and aliphatic and aliphatic

hydrocarbons, chlorinated hydrocarbons, ethers, esters, high molecular weight organic acids and alcohols, or lower molecular weight polyalkylene glycols.

42. The method of claim 39, wherein said plasticizer is selected from the group consisting of  
5 glycerin, sorbitol, maltitol, and mixtures thereof.

43. The method of claim 39, wherein said moisture retention agent is selected from the group  
consisting of celluloses, cellulose derivatives, starches, starch derivatives, vegetable gums, non-  
hygroscopic, mono-, di- and oligosaccharides, and silicon dioxide.

10

44. The method of claim 39, wherein said active material is selected from the group  
consisting of medicaments, vitamins, minerals, fruits, and herbals.

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US90/05578

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/64, 9/48

US CL : 424/456, 451

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/456, 451

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
BRS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, 4,935,243 A (BORKAN et al) 19 June 1990, col. 3, lines 20-38, col. 5, lines 38-60, Examples	1-44
Y	US 5,780,056 A (AKAMATSU et al) 14 July 1998, col. 4, lines 11-19	1-44

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*B\* earlier document published on or after the international filing date

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\*Z\* document member of the same patent family

Date of the actual completion of the international search

23 MAY 2000

Date of mailing of the international search report

20 JUL 2000

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

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